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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,118	11/13/2003	Toshiyuki Takai	671302-2002	8301

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,118	TAKAI ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *6-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on December 1, 2005 is acknowledged. The traversal is on the ground(s) that Groups I, II, II, V, and VII fall under the same class and would thus suggest that it would not be an undue burden on the Examiner to search and examine the claimed subject matters of these Groups (Applicant's Election, December 1, 2005, pages 3-4). This is not found persuasive because as indicated by the Restriction Requirement of November 2, 2005, while the methods of Groups II, III, V, VII commonly depend on the transgenic non-human animal of Group I, the methods of Groups II, III, and V are patentably distinct because they require different method steps. An *in vitro* method for screening for a promoter or suppressor of oligodendrocytes is methodically different from that of an *in vivo* method. Group V is drawn to a method for screening for therapeutic compositions using the transgenic non-human animal. This method is comprised of different steps than that used to identify promoters in an *in vivo* and an *in vitro* method. With regards to Group VII being drawn to a method of using the transgenic non-human animal to diagnose a neruopsychiatric disorder, the method steps used to diagnose are different from that used to identify promoters or a therapeutic composition. Because these method steps are different, the search for these methods is burdensome because they will require separate, non-coextensive searches. Regarding the issue that Groups II, III, and IV be rejoined Applicant's Election, December 1, 2005, page 4), while the Applicant indicates that a search of Group IV would also encompass a search of Groups II and III, the

Examiner does not find the argument persuasive because a method to screen for a promoter or suppressor *in vitro* does not necessarily depend on a method to screen for a promoter *in vivo* and vice versa. As such, while there is a relationship between the promoter/suppressors identified using the methods of screening for them, the difference between the methods of screening makes them patentably distinct. Regarding the issue of a species election (Applicant's Election, December 1, 2005, page 4), the Applicant indicates that there is a disclosure of relationship between the claimed species as the species are all types of neuropsychiatric disorders. Regarding this issue, the Examiner has reconsidered the species restriction as most of the listed species are symptoms of disease. The requirement is still deemed proper and is therefore made FINAL.

Claims 6-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 1, 2005.

Claims 1-5 are under consideration.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Pages 23-26 of the specification is a listing of references. If Applicant would like these references to be considered, they must be listed on an IDS and copies of the references must be provided.

Applicant filed an IDS on December 8, 2003. The listed references have been considered.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1 is drawn to a non-human animal model comprising a deficiency in chromosomal DAP12 gene function. This encompasses mice comprising a natural mutation in chromosomal DAP12, which is non-statutory matter. Adding "transgenic" to the phrase, "a non-human animal model" and changing "deficiency" to "disruption" would obviate the rejection. Claims 2-5 depend on claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising a homozygous disruption of DAP12 (DNAX Activation Protein 12) in its genome, wherein the mouse exhibits hypomyelination due to incomplete myelination,

does not reasonably provide enablement for

a non-human animal model of oligodendrocyte developmental disorders, wherein the non-human animal comprises a deficiency in chromosomal DAP12 gene function, and shows an oligodendrocyte developmental disorder.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

With regards to the broad scope of the claimed invention being drawn to any non-human animal, while the specification provides guidance on how to make a transgenic mouse comprising a disruption DAP12 of its genome, wherein the mouse exhibits hypomyelination in the frontal lobe of the cerebrum and the thalamus, the specification does not provide guidance on other knockout non-human animals which exhibit this phenotype. An artisan would need to know how to do this because at the time of filing, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al. 1992 Nature, 359: 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al., 1987 Nature, 326: 295-298 and Jaenisch, 1988 Science, 240: 1468-1474). As the art teaches unpredictability in making a mouse model of disease, the art indicates that an artisan cannot necessarily predict that a non-human model can necessarily be made. Thus, the invention is limited to mouse. In addition to this issue, the art of transgenesis is not advanced to the point that gene

disruptions can be routinely obtained for any variety of non-human animals. The art teaches that the only known animal in which targeted gene disruption can occur is the mouse. This is because mouse is the only animal in which ES cells can be generated and which chimerism from ES cells extend to the germline. According to Murray, et al., 1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61, the "isolation of ES cells has not been accomplished unequivocally in other species, including in domestic livestock (Murray, et al., page 59, lines 3-4)." Thus, the art teaches that making transgenic non-human animals via ES cells is limited to mice. The specification does not teach how to obtain other mammalian ES cells. For this reason, a skilled artisan is not enabled for other transgenic non-human animals made from ES cells.

With regards to the broad scope of the claimed invention being drawn to any oligodendrocyte developmental disorder, the scope encompasses all the many aspects of oligodendrocyte development. The specification teaches that there was less myelin basic protein (MBP) in the thalamus in the frontal lobe of the cerebrum, including the caudate nucleus in DAP12 knockout mice at 3 months and at 1.5 months of age (specification, page 13). The specification also teaches that the reduction of MBP observed in the mice is attributed to hypomyelinosis. As there were no signs of demyelination in the -/- mice, this suggested that the reason for the hypomyelination was incomplete myelination (specification, page 14). While the specification provides this guidance as to the pathology of the phenotype, the specification does not teach that DAP12 has roles in every and all aspects of oligodendrocyte development. For

example, the art teaches that an O-2A progenitor cell can differentiate into an oligodendrocyte or an astrocyte (Levine et al., 2001, Trends in Neuroscience, 24: 39-47, page 39, 2nd col., 2nd parag.). However, nothing in the specification indicates that DAP12 has any role in determining O-2A cell differentiation. In another example, Osterhout et al., 1997, J. of Neuroscience, 17: 9122-9132, page 9122, 1st col., 1st parag. teach that progenitor cells that arise in the subventricular zone and migrate through the brain parenchyma into axonal tracts and gray matter. Nothing in the specification indicates that DAP12 has any role in progenitor cell migration. With regards to the claims broadly encompassing all aspects of myelinogenesis, the art teaches that in addition to incomplete myelination which leads to hypomyelinosis, another myelin developmental defect occurs when the expression of proteolipid protein (PLP) is altered in oligodendrocyte. Changes in PLP levels lead to severe abnormalities of myelin formation (Porter and Tennekoon, 2000, Mental Retardation and Developmental Disabilities Research Reviews, 6: 47-58, page 49, 2nd col., 1st parag.). Porter and Tennekoon teach that the lack or overexpression of PLP leads to dysmyelination with poorly compacted myelin and abnormal periodicity (Porter and Tennekoon, page 49, 2nd col., 2nd parag.). Thus, the specification does not provide guidance for every and all aspects of oligodendrocyte and myelinogenesis development.

With regards to the claimed invention being drawn to a non-human animal model exhibiting a myelinogenesis developmental disorder and exhibits a neuropsychiatric disorder of dementia, while the specification teaches that 5 month old DAP12 knockout mice exhibit significantly lower levels of startle responses in general, as compared to

wild type mice in the prepulse inhibition (PPI) study (specification, page 18) and also showed significantly lower suppression levels of acoustic prepulse inhibition (specification, page 18), the specification does not teach that these responses are indicative of Huntington's disease. In the case of the claims encompassing Huntington's disease, the art teaches that this disease is a progressive neurodegenerative disorder, which means that this is not a disease that occurs from myelinogenesis (Geyer et al., 2002, Molecular Psychiatry, 7: 1039-1053; page 1044, parag. under "Huntington's Disease"). Thus, Huntington's disease cannot be encompassed by the claims.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Bakker et al., 2000, Immunity, 13: 345-353.

Bakker et al. teach that a DAP12-targeting vector comprising a 3kb Hpa I fragment containing exons 1 and II and a 3.5 Hind III fragment containing exon V were cloned into the vector in the opposite transcriptional orientation relative to the loxP-flanked neomycin-resistance gene. Exons 3 and 4, which encode the transmembrane region and part of the cytoplasmic region of DAP12, including the first tyrosine of the ITAM, were deleted by this strategy (Bakker et al., page 345, 2nd col. under "Generation of DAP12-Deficient Mice" to page 346, 1st col., 1st parag.). Bakker et al. teach that young adult DAP12-/- mice were normal with respect to viability, weight, fertility, growth, and gross anatomy (Bakker et al., page 346, 2nd col., 2nd parag.) and were remarkably resistant to disease (i.e. challenge with MOG peptide to induce experimental autoimmune encephalomyelitis (EAE)) when compared with their heterozygous littermates (Bakker et al., page 349, 2nd col., 2nd parag. to page 350, 1st col., 1st parag.).

While Bakker et al. do not teach that the DAP12 -/- mice exhibit any symptoms of Nasu-Hakola disease, such as systemic bone cists and progressive presenile frontal-lobe dementia resulting in death before 50 years of age, Bakker et al. teach that the pathology of Nasu-Hakola disease are of late onset. As such, Bakker et al. teach that they are examining the DAP12-/- mice as they age to see if feature of Nasu-Hakola disease occur. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily

or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, Bakker et al. anticipate claims 1-5.

Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Tomasello et al., 2000, Immunity, 13: 355-364.

Tomasello et al. teach a KARAP/DAP-12 knockin strategy in which the mutated KARAP/DAP-12 protein lacks the Y75 residue and wild-type C terminus amino acids (KΔY75 protein) (Tomasello et al., page 355, 2nd col., parag. under "Generation of KARAP/DAP12 Knockin Mice", see also Figure 1). Tomasello et al. teach that the KΔY75/ KΔY75 mice exhibit a major increase in the number of $CD11c^{+}DEC205^{-}$ dendritic cells (DCs) in the lamina propria of the mucosla villi, as well as in the subepithelial dome (SED), but not in the intrafollicular T cell region (IFR) of Peyer's patches (Tomasello et al., page 361, 1st col., 2nd parag. under "Myeloid Abnormalities in Absence of Functional KARAP/DAP-12"). Lack of functional KARAP/DAP12 also results in abnormally high numbers of MHC class II^{+} and $CD11b^{+}$ cells with dendritic

morphology in skin and buccal mucosa dermis Tomasello et al., page 361, 2nd col., 1st parag.).

While Tomasello et al. teach these characteristics exhibited by the KΔY75/ KΔY75 mice, they do not teach that the mice exhibit any symptoms of Nasu-Hakola disease. It is noted, however, that Tomasello et al. teach that it would be important to investigate whether KARAP/DAP-12-deficient patients present abnormalities within the myeloid compartment and whether such alterations are related to the Nasu-Hakola pathogenesis (Tomasello et al., page 361, under "Concluding Remarks"). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, Tomasello et al. anticipate claims 1-5.

Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Vivier et al. U.S. Patent Application, publication number US 2004/0045041, published March 4, 2004, priority date, September 20, 2000.

Vivier et al. teach a KARAP/DAP-12 knockin strategy for a mouse, wherein the mutated KARA/DAP12 protein lacks the Y75 residue and wild-type C-terminus amino-acids (KΔY75 protein) (Vivier et al., parag. 126). Vivier et al. teach that KΔY75/ KΔY75 mice exhibit a major increase in the number of $CD11c^{+}DEC205^{-}$ dendritic cells (DCs) in the lamina propria of the mucosal villi, as well as in the subepithelial dome (SED), but not in the intrafollicular T cell region (IFR) of Peyer's patches (Vivier et al., parag. 149).

While Vivier et al. teach these characteristics exhibited by the KΔY75/ KΔY75 mice, they do not teach that the mice exhibit any symptoms of Nasu-Hakola disease. It is noted, however, that Vivier et al. teach that it would be important to investigate whether KARAP/DAP-12-deficient patients present abnormalities within the myeloid compartment and whether such alterations are related to the Nasu-Hakola pathogenesis (Vivier et al., parag. 151). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and

compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, Vivier et al. anticipate claims 1-5.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH